Modern Concepts of Cardiovascular Disease

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ATHEROSCLEROSIS*

Atherosclerosis is one form of arteriosclerosis. It is the form that is most devastating since it is the chief cause of coronary disease and of cerebral vascular accidents. It is not a process of aging, and it is not inevitable. It is probably an episodic disease, and it is certainly (in part at least) a reversible one.

CHOLESTEROL - LIPID - LIPOPROTEIN METABOLISM AND ATHEROGENESIS

Alterations in cholesterol - lipid - lipoprotein metabolism play a decisive (but not exclusive) role in the pathogenesis of atherosclerosis. Without alterations in cholesterol - lipid - lipoprotein metabolism, clinically significant atherosclerosis is not likely to occur, regardless of the functional state of the cardiovascular system. In the presence of subtle or gross disturbances in cholesterol - lipid - lipoprotein metabolism, many other factors, local and systemic, may exert a significant influence on atherogenesis. For example, local injury or metabolic disturbances within the arterial wall may create a site of predilection for atherogenesis. Hypertension may also accelerate and intensify atherogenesis. Intramural hemorrhage in an atherosclerotic plaque, or ulceration and thrombus formation may convert a hitherto innocuous lesion into a clinically significant one. Therefore the processes of clotting and the factors influencing them are apparently important — even if only secondarily — in the induction of morbidity and mortality due to atherosclerosis. Furthermore, it is likely that the pattern of modern living, with its physical and emotional stresses, plays a determining role in the development of atherosclerotic disease and its sequelae.

Recognition of the multiplicity of factors influencing atherogenesis serves to highlight the complexity of the pathogenesis of this disease. However, it in no way negates the basic conclusion — arrived at on the basis of an overwhelming mass of factual data — that the key factor in the pathogenesis of atherosclerosis is altered cholesterol - lipid - lipoprotein metabolism. This fundamental concept serves as the foundation and point of departure of the recent research assault upon atherosclerosis — an assault which is greatly enriching our understanding of this disease and is pointing to an ultimate solution of this problem.

The cholesterol - lipid - lipoprotein concept of atherogenesis is rooted first of all in the classical studies of pathology and biochemistry, demonstrating that cholesterol-containing lipid complexes are the unique hallmarks of the atherosclerotic lesion. This concept is also based upon the longstanding observation that premature severe atherosclerosis is regularly encountered clinically in several disease states — e.g., essential familial hypercholesterolemia, the nephrotic syndrome, myxedema and hypothyroidism, diabetes mellitus, *et al.* — entities having but one feature in common, i.e., the supervention of chronic hypercholesterolemia. Similarly, recent data have conclusively demonstrated that a group of people with uncomplicated coronary atherosclerosis invariably exhibits alterations in cholesterol - lipid - lipoprotein metabolism compared with a matched clinically normal group.

THE EFFECTS OF DIETARY FACTORS ON ATHEROSCLEROSIS

In exploring the validity of the concept that the atherogenic process is a manifestation of disturbed metabolism, considerable attention has been recently focussed upon the effects of dietary factors on the organism. A large body of evidence has accumulated demonstrating that the life span pattern of diet exerts an important influence on the development of atherosclerotic arterial disease. Under the continuous assault of a high calorie, high lipid, high cholesterol diet, the organism's regulatory functions are apparently not fully adequate. Relative hypercholesterolemia becomes established, facilitating lipid deposition in the blood vessels. The usual American diet — a relatively recent innovation in nutrition, arising as a peculiar byproduct of civilization in general

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and our culture in particular — is such a continuing strain upon the metabolic processes. For further graphic illustration of the influence of dietary habit on plasma lipid patterns and atherosclerotic disease contrast the data on different ethnic groups — Italians, Spanish, Costa Ricans, Guatemalan Indians, Okinawans, Chinese, Japanese, Ceylonese, Bantu, *et al.*, who subsist on diets low in cholesterol and lipid, exhibit plasma lipid levels consistently lower than those of the inhabitants of the United States, and who are remarkably free of atherosclerotic disease. The suggested conclusion — of a relationship among life span pattern of diet, plasma lipid levels, and atherogenesis — is reinforced by data on diet-disease trends in Europe during World War II. In several countries a significant reduction in lipid intake, resulting from war conditions, was associated with a significant decline in death rates due to atherosclerotic disease. Similarly, many recent clinical studies in this country have conclusively demonstrated that plasma lipid levels may be significantly lowered by dietary means. (Long term studies are essential to ascertain definitely whether such dietary regimens are effective in preventing recurrences of myocardial infarction and prolonging the life of atherosclerotic patients.)

These facts do not justify any oversimplified idea that atherosclerosis is merely a problem of diet, pure and simple. In order to recognize the incorrectness of such a concept, all that is necessary is to consider a group of a thousand American males, aged 40, 50, or 60, who over the life span have ingested a typical American diet high in cholesterol and fat. Despite essentially identical patterns of food consumption, marked individual differences would undoubtedly be present within the group in morbidity and ultimate mortality due to atherosclerosis (although over 90% would exhibit gross anatomic evidence of atherosclerosis). Moreover, in defiance of any pure-and-simple dietary explanation of atherogenesis, the fact remains that women are remarkably immune to coronary atherosclerosis in the premenopausal decades — a phenomenon which can hardly be attributed to dietary differences.

What then is the role of diet? The ingestion over the years of a diet rich in cholesterol and lipid is apparently a prerequisite for the development of significant atherosclerosis in a population group. Such a diet is apparently an essential "trigger" for the atherogenic process (viewed as a group phenomenon). Once the trigger is pulled, individual differences — endogenous factors (determined hereditarily and otherwise) — come into play in influencing whether the charge is fired — i.e., whether the given person develops significant atherosclerosis. More correctly, the interrelationship is undoubtedly more complex, in that the nature of the given organism not only influences the response to diet, but the diet in turn influences the organism and its endogenous response to diet over the years.

This concept, of a profound interplay throughout life between organism and diet, between endogenous and exogenous, is the key to the understanding of such phenomena as the tendency for atherosclerotic disease to occur repeatedly among members of some families. Undoubtedly hereditary background may sometimes be decisive in determining the atherogenic effect of a high cholesterol-high lipid diet over the life span — a fact which has obvious clinical implications.

THE CONTRIBUTIONS OF ANIMAL EXPERIMENTATION

Knowledge derived from animal experimentation is one of the most important bases for the cholesterol-lipid-lipoprotein concept of atherogenesis. To appreciate fully the significance of the findings of experimental atherosclerosis, it is necessary to delineate its "pre-history." Prior to 1910, repeated experimental efforts to reproduce the lesion of human atherosclerosis in laboratory animals had met with consistent failure. In 1910-12 this objective was finally accomplished in rabbits by the feeding of cholesterol. In recent years atherosclerosis has been successfully induced in many laboratory animals — exclusively by procedures effecting an alteration in cholesterol-lipid-lipoprotein metabolism. Thus, atherosclerosis has been produced in chicks, rabbits, hamsters, and guinea pigs simply by cholesterol feeding; in dogs, by a combination of cholesterol feeding plus hypothyroidism; in monkeys and rats, by feeding high cholesterol, high fat, high choline diet, deficient in sulfhydryl-containing amino acids (with or without concomitant hyperlipemia-intensifying renal damage in rats); also in rats, by feeding a low-choline, high fat diet (without supplements of cholesterol); in geese, by force feeding (without supplements of cholesterol); in chicks, by inducing a sustained endogenous hypercholesterolemic hyperlipemia with estrogens (only aortic atherosclerosis results, without coronary lesions — *vide infra*). All the foregoing experimental regimens effect a chronic hypercholesterolemic hyperlipemia. Clearly, a disturbance in cholesterol-lipid-lipoprotein metabolism is a *sine qua non* for experimental atherogenesis!

The achievements of experimental atherosclerosis have made it possible to supplement clinical investigation with an extensive research assault in the laboratory, proceeding predominantly along two lines, the influence of diet and the role of hormones. With respect to the former, considerable work has been devoted to the possible influence of lipotropic factors on plasma lipid levels and atherogenesis. It is particularly important for clinicians to be familiar with the results of the many well controlled experiments

that have been done. These demonstrate conclusively that dietary supplements of lipotropic factors — including choline, inositol, methionine, vitamin B_{12}, vitamin E, various pancreatic factors, etc. — exert no significant influence on plasma cholesterol levels and atherogenesis. Neither clinical nor laboratory investigation affords any basis for the claim that lipotropic factors are effective, either prophylactically or therapeutically, against atherosclerosis.

More encouraging results have recently been obtained with defatted brain extract preparations as well as with plant sterols and other sterols closely resembling cholesterol in their chemical configuration. These materials, when fed to laboratory animals together with cholesterol, apparently prevent the gastrointestinal absorption of cholesterol, thereby inhibiting hypercholesterolemia and atherogenesis. The possible efficacy of such preparations in man is currently under investigation but has not been established.

STUDIES ON HORMONES AND ATHEROSCLEROSIS

Experimental atherosclerosis has also made significant contributions to our understanding of the endogenous factors, particularly hormones, influencing the pathogenesis of this disease. It is clear from a consideration of the disease in man that the endocrines exert a significant influence — a fact most suggestively illustrated by the marked relative immunity of premenopausal women to coronary atherosclerosis. Experimental work has shown that several of the endocrine systems may exert a significant influence on atherogenesis. Thus, for example, the thyroid hormones have a tendency to counteract the hypercholesterolemic and atherogenic action of cholesterol feeding in both rabbits and chicks. For reasons only poorly understood at the present time, these effects are incomplete and inconsistent. Experimentally induced disturbances in pancreatic function also effect cholesterol-lipid-lipoprotein metabolism and atherogenesis as do the steroids of the adrenal cortex.

It has been further demonstrated that experimental hypertension intensifies atherogenesis in animals with an atherogenic potential due to disturbances in cholesterol-lipid-lipoprotein metabolism. (Hypertension alone is not an adequate atherogenic stimulus.)

The most striking results obtained to date in studies on hormones and atherosclerosis would appear to be those with estrogens in chicks. Given either parenterally or orally to cholesterol-fed cockerels, estrogens prophylactically inhibit coronary atherosclerosis without exerting any effect on aortic atherosclerosis. This observation is significant first of all because of the lead it affords to the mechanism of the relative immunity of premenopausal women to coronary atherosclerosis. Furthermore, it is a clearcut experimental demonstration of the fact that atherogenesis proceeds according to different laws in different vascular beds — a basic conclusion supported by observations in man. In association with their effects on coronary atherogenesis estrogens also alter plasma lipid patterns, accentuating hyperphospholipemia, with resultant reduction of the plasma total cholesterol/lipid phosphorus ratio to or toward normal levels in cholesterol-fed chicks. The estrogens also induce significant changes in the ratio of alpha to beta lipoprotein in the plasma and in the spectrum of the plasma lipoproteins (as analyzed in the ultracentrifuge).

In subsequent experiments it was demonstrated that estrogens retain their effectiveness against coronary atherogenesis in depancreatized chicks and in cockerels with hyperadrenalism and steroid diabetes induced by administration of corticoids or ACTH. Moreover, the estrogens not only prevent coronary atherosclerosis but also inhibit the hypertension usually resulting from administration of desoxycorticosterone acetate or cortisone. It was also demonstrated that the feminizing effects of estrogens in cockerels can be prevented by simultaneous administration of androgens without interfering with the inhibitory action of exogenous estrogens on cholesterol-induced coronary atherogenesis. Further, the endogenous physiologic estrogen secretion of the egg-producing hen was shown to be equally effective in preventing cholesterol-induced coronary atherogenesis. Thus, sexually mature male and female chicks — like human beings — exhibit a significant sex difference in susceptibility to coronary atherosclerosis.

Since the foregoing experiments explored only the prophylactic potential of estrogens against cholesterol-induced coronary atherogenesis, further studies were done on their therapeutic effects. After feeding a cholesterol supplemented diet for several weeks (adequate to induce extensive coronary lesions), estrogen administration was instituted — with continued feeding of the atherogenic mash. Within a few weeks, the coronary vessels became practically free of lesions. The estrogens reversed both the lipophage and fibroblastic components of the coronary atherosclerotic plaques. Coronary atherosclerosis is a reversible process!

The findings of these studies afford the first experimental support for the hypothesis that estrogenic secretion may be a key factor in the mechanism of the relative immunity of premenopausal women to coronary atherosclerosis. Recent clinical investigations reinforce this concept and dovetail neatly with laboratory results. Thus, it has been shown that during the middle decades of life men and women have different plasma lipoprotein spectra (analyzed by chemical or ultracentrifugal methods) and that estrogens convert the male pattern to the female. Further, ovariectomy tends to render young women sus-

ceptible to coronary atherosclerosis. On the other hand, treatment with large dosages of estrogens seems to have a positive therapeutic effect on coronary atherosclerosis in elderly men with prostatic carcinoma.

Based on these significant observations in chick and man, an extensive clinical investigation was initiated by the authors almost two years ago on the possible efficacy of estrogens in the longterm treatment of human coronary atherosclerosis. Although results to date are promising, a definitive answer will not be forthcoming for another two to five years.

CONCLUSIONS

In conclusion, it is worth noting explicitly that the recent upsurge of clinical and animal research on atherosclerosis has already yielded several new possible approaches to the care of human atherosclerotic patients. Extensive clinical investigations are still necessary to determine whether these approaches will eventually find a proved place in general therapeutics. Such studies are proceeding with promising but not yet definitive results. Regardless of the specific results with any given approach, the general pattern of attack on the overall problem — proceeding within the context of the cholesterol-lipid-lipoprotein concept of atherogenesis — seems bound ultimately to produce a solution, including an effective approach to prophylaxis and therapy. Certainly, the progress of the last decade and the current activity in the field are a far cry from the hopeless, nihilistic attitudes to this disease process which destructively dominated medicine until recently.

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